

## Preface

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A major step in the evolution of eutherian mammals was the formation of the trophoblast, a specialised layer of cells derived early in embryogenesis. From this separate compartment, trophoblast is able to organise its own programme of development within a well-defined time span that is independent of the embryo, thereby enabling it to fulfil unique functions during ontogeny. While trophoblast contributes to the formation of the placenta in all eutherians, the manner by which it does so varies significantly among species (Carter 2001). It is important to recognise the pattern and extent of these variations if dialogue between investigators using human and those using animal material is to be meaningful. The trophoblast cell itself occurs in different forms ranging from uninuclear to multinuclear varieties, the latter appearing either as large giant cells or as a syncytium. Some of the giant cells are polytenic whilst others are polyploid but it is not known why these occur in different locations and time points of gestation in different species.

Trophoblast cells have remarkable growth and invasive properties *in vivo*, so much so that they resemble neoplastic cells, yet the *in vitro* culture and propagation of human trophoblast cells have still not met with much success. The recent realisation that some 'trophoblast' cell lines presently available are not what they seem to be has raised questions about how these cells should be characterised (King *et al.* 2000). Murine trophoblast stem cells have been identified, but in humans they have been elusive and the search continues.

Targeted mutation studies in mice have identified many genes involved in trophoblast development, some of which are specific to trophoblast, such as *Mash2*, a member of the basic helix-loop-helix gene family, while others also have roles in other cell lineages. It is becoming increasingly clear that different phases of trophoblast development are controlled by different regulatory genes (Rossant & Cross 2001). Interestingly, *Mash2* and the human equivalent *HASH2* show imprinting. Indeed, a significant number of imprinted genes so far identified are expressed in trophoblast (John & Surani 2000). The pattern of imprinting in trophoblast can differ from that in somatic tissues. An example of this is the selective inactivation of

the paternal X chromosome in trophoblast, while this process is random in somatic tissues. In marsupials, the paternal X chromosome is inactivated in all tissues so it appears that, with the evolution of eutherians, this selective process is retained only in extraembryonic tissues. Transcription and translation of endogenous retroviral genes have also been frequently observed in trophoblast (Taruscio & Mantovani 1998). What role these extraneous gene sequences might play in trophoblast development is not clear but the ability of one such retroviral protein (syncytin) to cause cell fusion and syncytialisation raises the intriguing possibility that they could contribute to trophoblast differentiation.

The term 'trophoblast' (Greek for nutrition) was introduced by Hubrecht (1889), who viewed it as a layer that serves to nourish the embryo. While this histiotrophic role is indeed important, there are many others, still poorly understood, that are equally critical for development. In spite of its physical separation early in ontogeny, trophoblast remains an important source of signalling molecules involved in embryonic patterning. Trophoblast also has influence on the mother. Its products regulate both the prenatal behaviour of the female (increased feeding, inhibition of sexual behaviour) and the production of milk by the mammary glands; it also primes the female's brain to ensure a prompt onset of maternal behaviour and milk let-down postnatally (Keverne 2001). Hence, its position at the interface between the fetus and its mother makes trophoblast a vital link in the pathway for maternal communication, with influence directed simultaneously at two genetically distinct individuals. The placenta separates the fetus and mother, so trophoblast must also hold the key to the immunological paradox of pregnancy, an enigma which has remained unexplained ever since the elucidation half a century ago, that transplant rejection is caused by genetic differences of polymorphic major histocompatibility complex (MHC) molecules between graft and recipient. In humans, trophoblast expresses a unique combination of MHC molecules and receptors for these paternally derived MHC molecules are expressed by a distinctive population of uterine leukocytes (natural killer cells) (Loke & King 2001). This provides a molecular mechanism for maternal recognition of the allogeneic trophoblast. In addition, the physiological transport of important molecules, such as antibodies, from mother to fetus is a selective receptor-mediated process by trophoblast. Thus, it is not surprising that trophoblast should have a range of functions far more varied than other tissues of the developing embryo.

The study of trophoblast, therefore, transcends disciplinary boundaries. Investigators interested in one aspect of trophoblast would greatly benefit from knowledge gained from research in areas other than their own. This became apparent recently when several of us at King's College, Cambridge discovered that although we have an overlapping interest in trophoblast, we are ignorant about the work being done by the others and would like to learn more from each other. For this reason, we have

gathered together scientists and clinicians from diverse disciplines to share their expertise in an intimate workshop environment characteristic of a Novartis Foundation Symposium. The presented papers and discussions are now published by Cambridge University Press and should serve as a valuable, comprehensive source of information for the future.

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